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VIEW POINTS

# Tumor suppressor microRNAs in lung cancer: An insight to signaling pathways and drug resistance

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**Abstract**

Lung cancer (LC) is the second common cancer for both women and men all over the world. Unfortunately, the number of LC deaths is increasing rapidly each year so early diagnosis of LC can be lifesaving. MicroRNAs are involved in multiple processes, such as cell differentiation, transcription, inflammation, proliferation, cell signaling, and apoptosis. In LC, microRNAs function as tumor suppressors (TS) or oncogenes depending on the targets. Changes in microRNAs expression level are related to tumor initiation, progression, and metastasis. MicroRNAs can regulate gene expression and thus affect the activity status of different signaling pathways including AKT, JAK-STAT, MAPK, TGF-β, WNT, and ERK signaling pathways. Positive or negative effects on drug resistance of LC are directly affected by microRNAs and their target genes. MicroRNAs can be beneficial in combination therapy with other drugs and chemotherapeutic agents for LC.

**KEYWORDS**

drug resistance, lung cancer, microRNA, signaling pathways, tumor suppressor

## 1 | INTRODUCTION

LC is one of the main reasons for cancer-related death in humans. Most cases of LC are identified at an advanced stage when cancer has previously metastasized and the chance for appropriate treatment is reduced.[1] There are two main types of LCs: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). About 15% of LC is SCLC, and about 85% is NSCLC. NSCLC contains lung adenocarcinoma (LUAD), large cell carcinoma (LCC) and lung squamous carcinoma (LUSC) subtypes.[2] Also, in both main types of LC, carcinoid tumors can occur in the lungs that account for 1% to 2% of human lung tumors.[3-5] In spite of significant advances in the treatment of LC, survival rates remain at 5 years because of the development of resistance to treatments.[6] The leading risk factor for LC is smocking and urban air pollution; nevertheless, only a small fraction of smokers develop LC which implies that other important factors may play a key role in developing LC, such as individual genetic variations and chemical agents.[7]

To date, despite the study of LC genetics and advancements in treatment and diagnosis, LC death rate has increased. The main reason for the poor prognosis and the low survival rate is the advanced stage with metastasis in most cases of LC at the time of presentation. There are different kinds of techniques for detection of LC. Some of these techniques are Narrow Band Imaging, Optical Coherence Tomography, Surgical Biopsy and Bronchial Genomic Classifier, Biopsy and Bronchial

  

Genomic Classifier is a novel diagnosis technique with the gene expression analysis.[8] Furthermore, Epigenetic biomarkers are one of the innovative and useful methods for early diagnosis and detection of various cancers that has been confirmed in the previous research.[9] Many studies revealed the importance of regulatory mechanisms at the posttranscriptional or translational level, for example, gene regulation by noncoding RNAs such as microRNAs. These mechanisms include regulation of different genes that mediate processes like cell cycle, inflammation, apoptosis, stress responses, invasion, and differentiation.[10]

MicroRNAs are a class of extremely conserved, small (19-25 nucleotides in length) single strand noncoding RNA molecules that can negatively regulate different gene expression at the posttranscriptional or translational level on the basis of their function in RNA silencing by base-pairing with complementary mRNA molecules and leads them to the inhibition of translation through mRNA degradation. Three processes can silence mRNA molecules: (1) degradation of the mRNA, (2) Reducing mRNAs sustainability by shortening its poly (A) tail, and (3) reducing the translation efficiency of mRNA. MicroRNAs involve in different cellular processes, such as transcription, cell growth, proliferation, inflammation, cell mobility, differentiation, apoptosis, and cell cycle.[11] They are usually encoded by the 3′-untranslated region (3′-UTR) or introns of genes which transcribed to a primary microRNA (pri-microRNA). *Drosha*, which encodes a ribonuclease (RNase) III double-stranded RNA-specific ribonuclease processes the pri-miRNA within the nucleus to a precursor microRNA (pre-microRNA). After nuclear processing, pre-microRNAs are transported to the cytosol by EXP-5. Next pre-microRNAs are cleaved and activated by the Dicer complex which is a multi-domain ribonuclease (RNase III-type) and loaded onto the Argonaute (AGO) protein, which is highly conserved protein between species, to generate the RNA-induced silencing complex (RISC; Figure 1).[12]

One microRNA has the ability to regulate multiple genes. On the other hand, a single gene can be regulated by different microRNAs. Thus, a single microRNA can regulate the expression level of several proteins.[13] MicroRNA plays a main regulatory role in gene expression and different biological processes which makes them one of the most relevant determining factors of cancer biology.[13-15] MicroRNAs act as tumor suppressor genes (TSG) or oncogenes so the altered expression of them is related to several human cancers and tumors.[16,17]

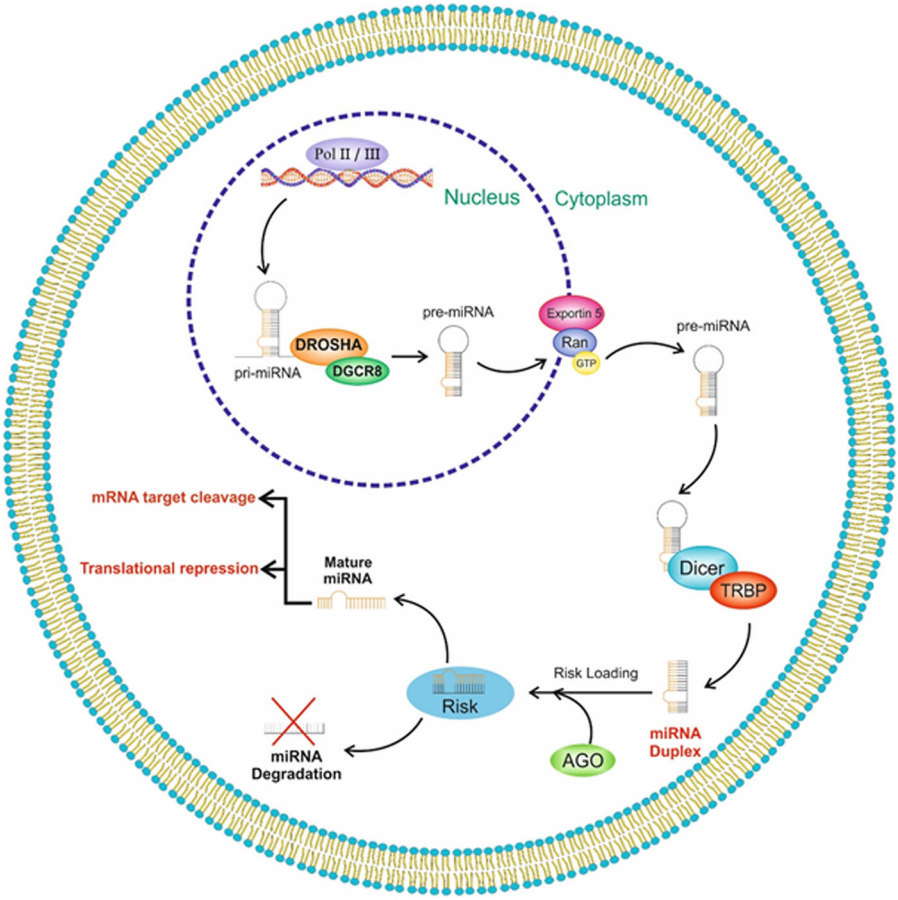


**FIGURE 1** Biogenesis and function of microRNA. Biogenesis of microRNA starts with the generation of the pri-miRNA transcripts by RNA pol II/III. The microprocessor complex, comprised of DGCR8 and Drosha, cleaves the pri-miRNA to generate the pre-miRNA. Then, the pre-miRNA is exported to the cytoplasm through Exportin5/RanGTP. Next pre- microRNAs are cleaved and activated by the Dicer complex (Dicer and TRBP). Finally, strands of the mature microRNA duplex are loaded into the Argonaute to produce the RISC. Mature microRNA leads to translational repression or mRNA target cleavage. RISC, RNA-induced silencing complex

Start and progression of diseases or malignancies, such as LC are frequently related to aberrant regulation of microRNA expression. Various microRNAs play key roles in LC pathogenesis and have the potential to be therapeutically targeted molecules and diagnostic markers. Therefore, investigation of the role of microRNA molecules may lead to an improved understanding of lung carcinogenesis and shed light on the therapeutic strategies and effective diagnostic to manage LC.[2,18]

Genetic alternations in TSGs and oncogenes are related to different cancers. Current data demonstrate that microRNAs also contribute to tumor development and formation indicating that microRNAs can act as TS or oncogenes (oncomir). Furthermore, tumor-associated microRNAs can serve as proper biomarkers for tumor prognosis and diagnosis.[19]

A proto-oncogene is a normal gene with the normal and necessary function that could turn into an oncogene because of increased expression or various mutations. Proto-oncogenes code some proteins which regulate differentiation and cell growth. An oncogene is a mutated gene that has a high potential to cause different cancers. Oncogenes are expressed at high levels or often mutated in cancer cells. Oncogenes are the main factors of tumor growth and directly regulate metabolic signaling pathways.[20] Overexpression or amplification of microRNAs may downregulate TSGs or other genes, which involved in cell differentiation. MicroRNAs take part in tumor formation through stimulating invasion, proliferation, and angiogenesis acting as oncogenes in different cancers.[21]

TSG or anti-oncogene is a protective gene that usually limits the growth of cancer cells. At the cellular level, TSGs are recessive. Therefore, inactivation of both alleles is necessary for cancer development. This is often done through mutation in first allele and deletion in the second allele. In some cases, the second allele is targeted by mutation, deletion or methylation and is led to the loss of expression. Some mutations deactivate both alleles in one event. These mutations are called dominant negative mutations. Loss of function of TSGs inclines a cell to neoplastic transformation.[22] MicroRNAs can act as TS or oncogenes depending on whether microRNAs target TSG or oncogenes (Figure 2).

TS microRNAs are frequently under-expressed in tumors and cancer cells. For example, *microRNA-15, microRNA-16*, and *let-7* are deleted or downregulated in leukemia and LC, but oncomirs, such as *microRNA-155* and *microRNA-21*, are overexpressed in tumors.[23] In a different type of cancer, overexpressed microRNAs might act as oncogenes, which promote cancer cell development through negatively regulating TSGs and other genes that control cell proliferation and apoptosis. On the other hand, under-expressed microRNAs in different cancers

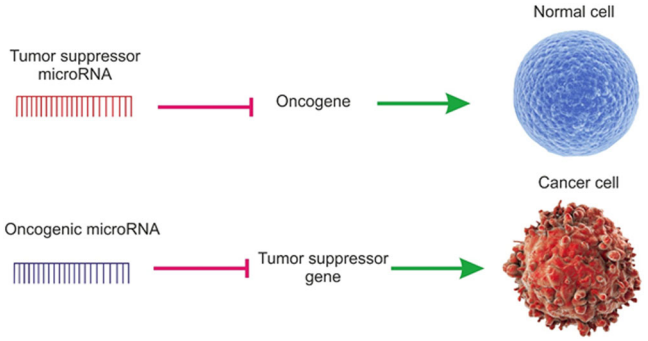


**FIGURE 2** TS microRNA vs oncogenic microRNA. MicroRNAs can act as TS by targeting oncogene, which leads to the development of normal cells or act as oncogenic microRNA (OncomiR) by targeting TSG, leads to the development of cancer cells. TSG, tumor suppressor genes

function as TSGs and might prevent cancer by regulating oncogenes and other genes, which control different cellular process.[24,25] The findings of the research indicated that microRNAs act as oncomirs through targeting TSG or act as tumor suppressive microRNA through targeting oncogene. Some TSGs or oncogenes may activate microRNAs transcription through binding to promoter regions of microRNAs target genes. Epigenetic changes (mainly methylation) and mutations in microRNAs target genes, regulate microRNA expression by TSGs and oncogenes.[26] Abnormal expression of microRNAs regulates oncogenic genes or TSGs expression, which leads to accurate detection of cancer.[27]

In this study, we will review the involvement of diverse TS microRNAs and the function of their targets in different types of LC in detail. Moreover, we will define their mechanism of action in different signaling pathways and review the functions of these microRNAs in the development of LC drug resistance.

## 2 | TUMOR SUPPRESSOR microRNAs

### 2.1 | MicroRNA-7

MicroRNA-7 (miR-7) is an important microRNA that extremely conserved among various species. In human species, *miR-7* expression stems from three different genomic loci: *mir-7-1, mir-7-2,* and *mir-7-3. mir-7-1* is located in the intron of *HNRNPK* gene on 9q21, hsa-*mir-7-2* is in the intergenic region of 15q26 and *mir-7-3* is in the intron of the *PGSF1a* gene on 19p13. *miR-7* is involved in several human diseases and the normal development of cells.[28]

*miR-7* is involved in different cellular process, such as cell growth, invasion, and migration of several tumors, such as LC and breast cancer.[29]

*PSME3* is one of the direct target gene of *miR-7* that is located in 17q21.31. *PSME3* is also called *PA28gamma,* which is a subunit of the 11 S REG-gamma and regulator of the 20 S proteasome. In addition, *PSME3* involve in cell growth and proliferation. MicroRNA-7 acts as a TS microRNA by negative regulation of *PSME3* expression in SCLC. *PSME3* is significantly upregulated and *miR-7* is downregulated in NSCLC cells particularly in LUSC and LUAD. Downregulation of *miR-7* might be associated with the tumorigenicity of NSCLC. Overexpression of *miR-7* and silencing of *PSME3* simultaneously downregulated the expression level of *cyclin D1* (*CCND1*) that leads to inhibition of NSCLC cells growth and proliferation. The *CCND1 gene,* as a regulatory factor of the cyclin D1-CDK4 (DC) complex, encodes the cyclin-D1 protein.[30,31]

In recent research, Xiong et al[32] studied the over-expression of *BCL-2* in NSCLC cells. The expression of *BCL-2* at transcriptional and translational levels in NSCLC is downregulated by *miR-7* through direct interactions with 3′-UTR of the *BCL-2* gene (Figure 3). The BCL-2 family of proteins is an essential factor for the regulation of the apoptosis and mainly is found in mitochondria, which is the chief controller of extracellular and intracellular signals. The members of this family are divided into two main groups including one with antiapoptotic roles, such as Bcl-XL and BCL-2 and the other with proapoptotic roles like BCL2 Associated X Apoptosis Regulator (Bax) and Bid. Therefore, *miR-7* downregulates *BCL-2* and it might be involved in the proapoptotic function of *miR-7* in NSCLC cells.[32]

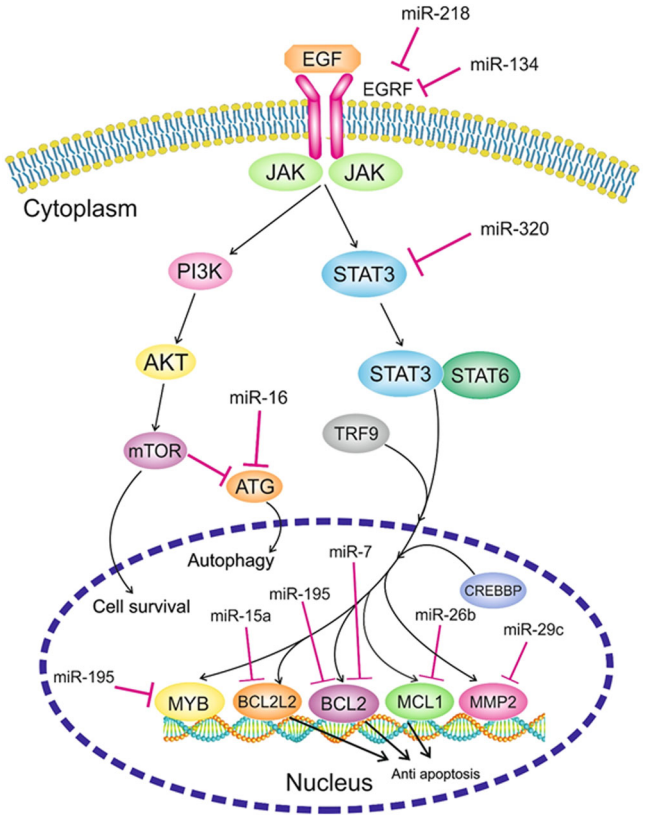


**FIGURE 3** EGFR, JAK-STAT, m-TOR, AKT, and related signaling pathway and microRNA in lung cancer. EGFR, epidermal growth factor receptor

*miR-7* directly targets Paired box 6 (*Pax6*) in the NSCLC (Figure 4). *Pax6* is a conserved transcription factor (TF), which involve in embryogenesis and development of endocrine glands. *Pax6* and *miR-7* mediate the activities of the ERK/MAPK signaling pathway. In NSCLC cells, *Pax6* is significantly upregulated, whereas *miR-7* expression is downregulated so overexpression of *miR-7* can reduce the expression level of *Pax6*, which leads to inhibition of NSCLC cells development.

*miR-7* directly targets protein tyrosine kinase 2 (*PTK2*) that encodes Focal adhesion kinase protein (FAK) through the ERK/MAPK signaling pathway in NCSLC cells (A549, H1299, and H1355; Figure 4). FAK is a non-receptor tyrosine kinase, which involves regulation of cell migration, apoptosis, and proliferation. In addition, the expression of FAK proteins is inhibited by *miR-7*. However, the expression of FAK proteins is positively related to the expressions of MAPK and ERK, representing that the ERK/MAPK signaling pathway inhibited by *miR-7* through directly targeting *PTK2* in NCSLC cell.[33]

## 2.2 | MicroRNA-15a & MicroRNA-16

miR-15a and miR-16, which both are located on 13q14, involve in cell cycle control and apoptosis. miR-15a/16 are frequently downregulated in LUSC and LUAD cells. The expression level of miR-15a/16 negatively associates with the expression level of CCND1 in LUSC and LUAD tumors. The normal expression level of miR-15a/16 directly regulates CCND1, cyclin D2 (CCND2), and cyclins E1 (CCNE1) in NSCLC cell lines. Interestingly, cell cycle arrest in G1-G0 is induced by overexpression of miR-15a/16 in NSCLC.[34]

In NSCLC, miR-15a is significantly downregulated. miR-15a directly targets BCL2L2, which is an antiapoptotic (pro-survival) member of the Bcl-2 family of proteins and acts as an important oncogene in NSCLC. The expression level of BCL2L2 is increased in different kinds of malignancies including gastric cancer and LC. The high expression level of BCL2L2 in different cancer cells increased their invasion and migration by activating the PI3K/Akt signaling pathway. Tumor stage, poor prognosis, and differentiation status of LC are associated with overexpression of BCL2L2. By targeting BCL2L2, the high expression level of miR-15a can reduce the cell

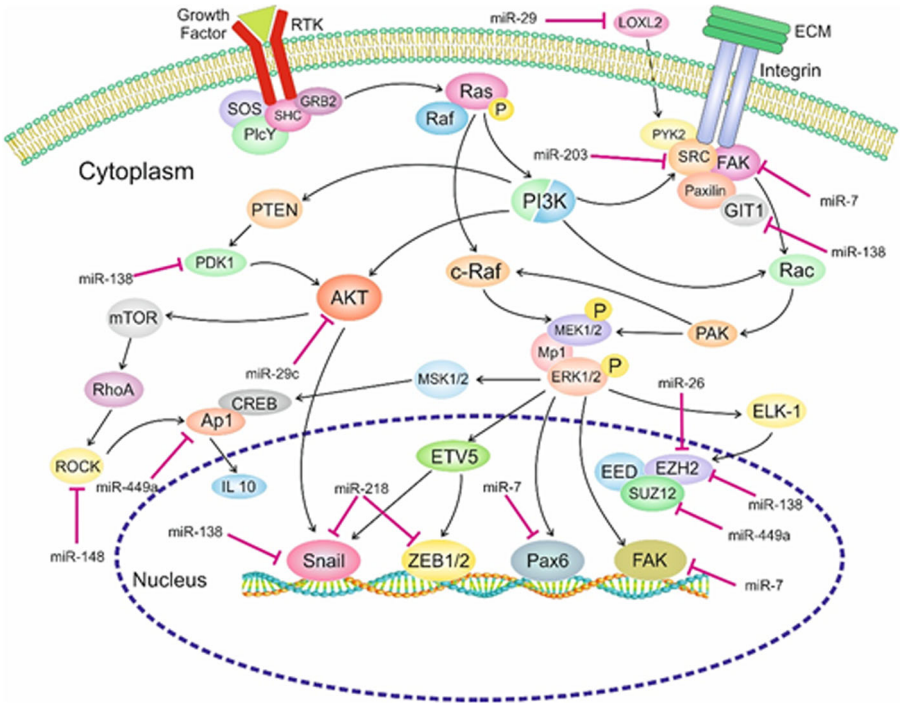


**FIGURE 4** MAPK/ERK, FAK, AKT, and related signaling pathway and microRNA in lung cancer

growth via repression of apoptosis and inhibit cell migration in NSCLC cells (Figure 3).[35,36]

miR-15a/16 and miR-34 contain very distinct seed sequences but they are associated functionally. miR-15a/16 and miR-34 share the same targets including CCND1, Bcl-2, and E2F3. However, miR-15a/16 have other targets that are unique, such as CCNE1, CCND2, and cyclin D3 (CCND3). In a complex, Cyclin D with Cyclin-dependent kinase 2 (CDK2) regulate the progression of the cell cycle through the boundary of the G1 phase to the S phase. These complexes phosphorylate Retinoblastoma (Rb) protein and phosphorylation of Rb protein inhibit it from binding to E2F, which is an important TF and drives cells from the G1 phase to the S phase. Finally, the cell cycle arrested in G1-G0 is induced by miR-15a/16 in NSCLC cells.[37]

Li et al[38-40] shows that low expression level of miR-15a enhances cell invasion and proliferation of NSCLC cells. Furthermore, downregulation of this microRNA in NSCLC cells decreased the expression of E-cadherin, although increased those of vimentin and N-cadherin. Cadherins are important in the formation of adherens junctions. furthermore, E cadherin is an Epithelial Mesenchymal Transition associated (EMT) protein. EMT is a biologically highly dynamic process that epithelial cells miss their polarity and cell to cell adhesion, and gain immigration feature and invasive properties to become mesenchymal stem cells. It occurs during normal embryonic development, wound healing, organ fibrosis, and tissue regeneration. A main feature of EMT is the upregulated expression level of vimentin and N-cadherin and the low expression level of E-cadherin. The low expression level of miR-15a leads to an increase in the expression of vimentin and N-cadherin and able to downregulate the expression level of E-cadherin. These proofs suggest that the expression level of E-cadherin in NSCLC cells may be related to the downregulated miR-15a on the EMT. In conclusion, the low expression level of miR-15a in NSCLC cells promotes EMT and its overexpression inhibits EMT.

miR-16 is important in regulating cell differentiation and self-renewal. *miR-16* downregulated in NSCLC, LUAD, and LUSC cells. *miR-16* directly targets Autophagy-related 3 (ATG3), which is involved in autophagy of NSCLC cells (Figure 3). In patients with NSCLC, ATG3 is significantly upregulated and *miR-16* is significantly downregulated. ATG3 and *miR-16* are involved in the TGF-β1-modulated NSCLC cell function. TGF-β1 is essential for the induction of EMT and regulating autophagy-induced EMT. In conclusion, TGF-β1-induced EMT is inhibited by *miR-16* in NSCLC cells by activation of autophagy through regulating ATG3.[41,42]

## 2.3 | MicroRNA-26

*The microRNA-26* family includes three members of *miR-26a-1*, *a-2,* and *b*. *miR-26a-1/2* have an identical sequence, which differs from the *miR-26b*. Zhu et al[43] indicated that that *miR-26* family blocks G1 to the S phase transition in LC. Solomides et al[44] demonstrated that *miR-26* is downregulated in different cancers, such as hepatocellular carcinoma and NSCLC.

The *miR-26* family can directly target different genes and regulate important pathway. For instance, *miR-26b* can directly target *Mcl-1* in SCLC cells (Figures 3 and 5). *Mcl-1* is an important antiapoptotic member of the Bcl-2 family of protein. *Mcl-1* is expressed at a high level in human cancers and suppressed by *miR-26b*.[45,46]

*miR-26b* directly targets and regulates Migration and invasion enhancer 1 (*MIEN1*) expression in NSCLC cells. *MIEN1* is also called *ORB3* or *C35*, located in the chromosome 17, encodes MIEN1 protein, which is of primary importance in the regulation of apoptosis, through controlling of caspase-3 (CASP3) and its overexpression increases cell migration. In NSCLC cells, *miR-26b* targeted *MIEN1* through the NF-κB/MMP-9/VEGF signaling pathway and inhibited cell migration and invasion. NF-κB is a TF that controls cell survival and production of cytokine. Matrix metalloproteinase 9 (*MMP-9*), which is a downstream target gene of the NF-κB pathway, is involved in the migration of NSCLC cells. *MIEN1* changes *MMP-9* expression levels by regulating the NF-κB pathway. In conclusion, the expression level of *MMP-9* and NF-κB are increased by overexpression of *MIEN1*.[47-49]

*miR-26a* regulates Lin-28 homolog B (*LIN28B*) via direct binding of its 3′-UTR in NSCLC cells. *LIN28B* is a suppressor of microRNA biogenesis also known as an oncogenic driver that is intensely upregulated in NSCLC compared with normal cells. Overexpression of *miR-26a* reduces *LIN28B* expression. Inhibited *LIN28B* leads to an upregulation of *STAT3* and Interleukin 6 (IL6) and balances the enhancement of invasion and metastasis in NSCLC cells. Remarkably, the expression of *STAT3* and *IL6* are decreased by silencing *LIN28B* in NSCLC cells. In conclusion, *LIN28B* is one of the main target genes of *miR-26a* and main downstream mediators of *LIN28B* are *STAT3* and *IL6* in the LC cell metastatic processes.[50,51]

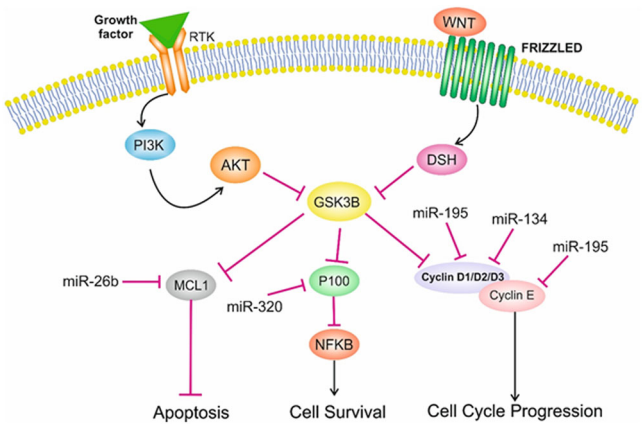


**FIGURE 5** RTK and Wnt signaling pathway and microRNA in lung cancer

*miR-26a/b* inhibits migration, invasion, and proliferation of LC cells by targeting cell division cycle 6 (*CDC6*) in LC cells directly. *CDC6* is an important factor for loading the helicase minichromosome maintenance protein complex (MCM) proteins onto replication origins. *CDC6* encodes Cell division control protein 6 homolog that participates in checkpoint controls. Regulation of replication-initiation proteins is not only critical for preventing cancer but also vital for certifying genetic inheritance in normal cell cycle progression. *miR-26a* and *miR-26b* certainly suppress *CDC6* gene expression by binding to 3′-UTR of the *CDC6* gene that inhibits LC cells development through preventing the loading the helicase MCM proteins onto replication origins.[52]

## 2.4 | MicroRNA-29

*The microRNA-29 (miR-29)* family includes three members of *miR-29a, b*, and *c*. Abnormal expression of all *miR-29* family members, which have anticancer roles, has been observed in various cancer cells.[53,54]

*miR-29* family can target Lysyl oxidase-like 2 (*LOXL2*) in LUSC directly (Figure 4). *LOXL2* is a well-known oncogene and an enzyme that changes the structure of histones and, therefore, changes the shape of the cells, which leads to metastasize of cancer cells. Furthermore, overexpressed *LOXL2* is confirmed in LUSC cells and silencing of *LOXL2* inhibited invasion and migration of LUSC cells.[55]

Wnt signaling pathway is suppressed by the *miR-29* family through demethylation of Wnt inhibitory factor-1 (*WIF-1*) in NSCLC (Figure 6). DNA methyl-transferases (*DNMTs*) are a group of enzymes cause the abnormal DNA methylation of TSGs which methylate CpG residues. Tan et al[56] have reported overexpression of *DNMT3A, DNMT3B*, and *DNMT1* in different types of cancers. *DNMTs* overexpression is correlated with hyper-methylation of TSGs.

*miR-29c* downregulates *MMP2* and integrin beta-1 (*ITGB1*) directly by targeting the 3′-UTR sequence which reduces the protein levels of *ITGB1* and *MMP2*. The *MMP2* gene encodes a protein called 72-kDa type IV collagenase, which involve in migration, proliferation, invasion, and adhesion. *miR-29* can reduce the *MMP2* enzyme activity by binding to its 3′-UTR site, which leads to suppression of LC cell adhesion to the extracellular matrix (Figure 3).[57]

*miR-29c* acts as a TS by targeting vascular endothelial growth factor A (*VEGFA*) in LUAD (Figure 6). *VEGFA* is involved in endothelial cell growth and angiogenesis. Overexpression of *VEGFA* promotes cell migration and inhibits apoptosis. Recent studies indicated that *VEGFA* is overexpressed in many cancers including LC and contributes to

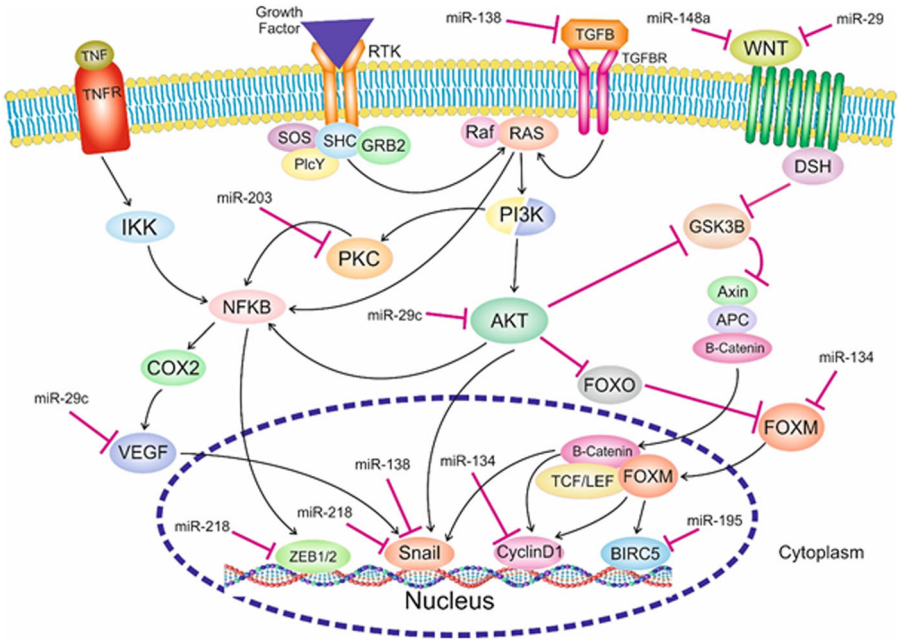


**FIGURE 6** Wnt, TGFB, RTK, TNFR, MAPK/ERK, AKT, and related signaling pathway and microRNA in lung cancer

poor prognosis. *MiR-29c* targets *VEGFA* as a downstream gene and acts as a TS microRNA in LUAD.[58]

AKT Serine/Threonine Kinase 2 (*AKT2*) is an important oncogene which is targeted and is negatively regulated by *miR-29c* (Figures 4 and 6). Overexpression of *AKT2* has been reported in different cancers, such as LC. Therefore, *miR-29c* acts as a TS microRNA in LC. *AKT2* is serine/threonine-protein kinases also is called the RAC-beta serine/threonine-protein kinase or AKT kinase. *AKT2* regulates different cellular processes including proliferation and angiogenesis.[59]

## 2.5 | MicroRNA-134

*miR-134* is found on chromosome 14q32 and is dysregulated in various cancers, for instance, glioma, breast, colorectal, and LC. *miR-134* is a well-established TS microRNA. Abnormal expression of *miR-134* has been reported in various human cancers, such as ovarian and LC. *miR-134* also involve in tumor cell invasion, metastasis, drug resistance, proliferation, and apoptosis.[60] The aberrant expression of *miR-134* is related to EMT phenotype and invasion of NSCLC cells. Li et al[61,62] indicate that EMT is inhibited by *miR-134* in NSCLC cells. Furthermore, Forkhead box protein M1 (*FOXM1*) is a functional and direct target of *miR-134* (Figure 6). *FOXM1* is an oncogenic gene and a potential metastasis promoter. Most significant molecular markers of EMT are gain of Vimentin and loss of E-cadherin expression. Many studies indicate that microRNAs act as essential modulators for EMT. Moreover, Knockdown of *FOXM1* through *miR-134* reverses EMT in NSCLC cells. *FOXM1* is one of the important members of forkhead box TFs family which takes part in TGFb1-induced EMT in NSCLC cells. Overexpression of *FOXM1* is related to invasion and early steps of metastasis of human LC.

*miR-134* can inhibit NSCLC colony formation, proliferation, invasion, migration, and stimulated cell apoptosis through targeting 3′-UTR of the *CCND1*; Figures 5 and 6). *CCND1* gene encodes Cyclin D1 protein, which is an oncogene that revealed a lot of oncogenicity power through the increase of migration, invasion, and EMT.[63] *ITGB1* is a direct and functional target of *miR-134* in NSCLC cells. *ITGB1* is a cell surface receptor and is involved in angiogenesis and promoting endothelial cell motility. *miR-134* downregulates *ITGB1* expression and inhibits EMT in NSCLC cells.[64]

*miR-134* targets the epidermal growth factor receptor (EGFR) directly in NSCLC cells (Figure 3). The *EGFR* belongs to the ERBB family, which activates different signaling pathways to convert extracellular signals into proper cellular responses. *EGFR* is often abnormally activated in different cancers, such as NSCLC. *EGFR* signaling includes three main signal transduction pathways, which are RAS/RAF/MEK/ERK, STAT3-dependent signaling, and PI3k/AKT. In NSCLC, *miR-134* downregulates *EGFR* and suppresses specific *EGFR*-associated signaling. *miR-134* inhibits growth and proliferation of LC cells by cell cycle arrest and induces cell apoptosis through targeting of *EGFR*.[65]

## 2.6 | MicroRNA-138

*miR-138* is an extremely conserved microRNA amongst mammals.[66] Among the microRNAs, *miR-138* has recently appeared as a significant TS in various cancers,

such as osteosarcoma, and NSCLC. *miR-138* induces apoptosis, inhibits proliferation, invasion, metastasis, and increases chemo-sensitivity of LC cells through the inhibition of several targets.[67]

In NSCLC cells, *mir-138* significantly downregulated and interestingly, upregulation of *miR-138* can inhibit cell growth through targeting *EZH2* which is a functional and direct target of *mir-138*. *EZH2* is responsible for the methylation activity of a complex, which includes EED, SUZ12, and PCL. These are the group proteins that are required for optimal function of EZH2. In addition, the expression level of *EZH2* is reduced by overexpression of *mir-138* in NSCLC. The binding site of *mir-138* is recognized in the 3′-UTR of *EZH2* mRNA (Figure 4).[68,69]

*miR-138* is identified as potential TS that regulates *PDK1* expression in NSCLC cells (Figure 4). *PDK1* is involved in different processes including differentiation, apoptosis, and cell proliferation. Furthermore, *miR-138* can inhibit proliferation of NSCLC cells by targeting *PDK1* which suggests the key role of *miR-138/PDK1* cascade in NSCLC.[70]

Upregulation of *miR-138* inhibits cell division and growth in NSCLC. Cyclin D3 (*CCND3*) is one of the target genes of *miR-138*. Cyclin D3 is a member of the cyclin D family, which involve in the G to S transition in the cell cycle. Upregulation of *miR-138* leads to repression of *CCND3* in NSCLC cell lines that suppresses G to S transition in NSCLC cells.[71]

*miR-138* overexpression induced the reversion of EMT with increased E-cadherin and *ZO-1* expressions and reduced Slug (*SNAI2*) expression accompanied by reduced invasion and migration capabilities. The *SNAI2* gene encodes a protein with nucleic acid binding fingers, which acts as a transcriptional repressor in different cancer cells. SEMA4C (Semaphorin 4C) and *GIT1* are direct and functional targets of *miR-138*, both critical for the development of NSCLC EMT (Figures 4 and 6). *SEMA4C* is a protein-coding gene that encodes an important member of the Semaphorin family of proteins having various functions in immune cell regulation, tumor progression, and vascular growth. The *GIT1* gene encodes ARF GTPase-activating protein GIT1 that is an enzyme involved in phosphorylation and inhibition of the Adrenoceptor Beta 2 (*ADRB2*).[72]

*miR-138* is an upstream regulator of forkhead box P4 (*FOXP4*) in NSCLC cells. Overexpression of *miR-138* suppresses *FOXP4* at the transcription level. Many members of the Forkhead box (*FOX*) gene family, including *FOXP4*, have roles in human oncogenesis. All members of the forkhead box family have a forkhead domain (FKH) that acts as a transcriptional repressor or activator. *FOXP4* is independently related to the *miR-138* regulatory pathway in NSCLC cells.[73]

## 2.7 | MicroRNA-148

The *mir-148/152* family is composed of three extremely conserved microRNAs including *mir-148a, b, and mir-152*. Mature microRNA is generated from *mir-148/152* family has similar structures, sequences, and an identical seed region. In humans, *mir-148a, mir-148b, and mir-148b are located in* chromosomes 7p15.2, 12q13.13, and 17q21.32, respectively.[74] The downregulated expression of *mir-148a* can be detected in different cancers, such as colorectal cancer and NSCLC.[75]

Chen et al[76] show that Wnt family member 1 (*Wnt1*) is a functional and direct target of *mir-148a*. The Wnt signaling pathway regulates critical features of cell destiny determination, cell migration, polarity, and organogenesis during embryonic development. *mir-148a* expression correlates negatively with the expression of Wnt1 in LC. Furthermore, the expression of Wnt1 protein is inhibited by overexpression of *mir-148a*, which reduces cell invasion and migration in LC cells (Figure 6).

*ROCK1* is a potential metastasis promoter, which is directly targeted by *miR-148a* (Figure 4). ROCK1 protein is a serine/threonine kinase and is a key member of the Rho family of GTPase proteins. *ROCK1* is widely upregulated in NSCLC and is negatively correlated with *miR-148a* expression. *miR-148a* reduces the expression of ROCK1 protein, which leads to a decrease in cell invasion and migration and reversed EMT in NSCLC cells.[77]

*miR-148b* involves in cancer progression and tumorigenesis. *miR-148b* suppresses the invasion, migration, and proliferation of NSCLC cells through directly targeting Carcinoembryonic antigen (*CEA*) pro-oncogene. *CEA* encodes a cell surface glycoprotein that is a member of the *CEA* family of proteins. CEA protein promotes tumor development through its role as a cell adhesion molecule. Moreover, CEA protein regulates cell polarity, apoptosis, and differentiation. *CEA* is upregulated in NSCLC specimens and its mRNA levels are negatively associated with *miR-148b* expression.[78]

## 2.8 | MicroRNA-195

*miR-195* is a member of the *miR-15/16* family, which includes five microRNAs (*miR-15a, miR-15b, miR-16-1, miR-16-2, and miR-195*). Many studies have reported that *miR-195* has diverse effects on cell growth and apoptosis in different cancers, such as LC. Abnormal expression of *miR-195* has been reported in various cancers, such as gastric cancer and NSCLC.[79-81]

*miR-195* acts as TS microRNA in NSCLC through directly targeting *Bcl-2, CCNE-1*, and MYB proto-oncogene, transcription factor (*MYB*), and negatively regulating their expression (Figures 3 and 5). *Myb* genes are

members of a large gene family of TFs found in animals and plants. In humans, *Myb* genes contain two main members including Myb proto-oncogene like 1 and Myb-related protein B. *CCNE-1* is an important oncogene and involve in cell proliferation and oncogenesis. *miR-195* is downregulated in NSCLC cells but its overexpression results in reduced *MYB, BCL2* and, *CCNE1* expression, which leads to suppression of NSCLC cells development.[81]

*miR-195* regulates apoptosis, cellular senescence and cell cycle progression of NSCLC cells. *CCND3* is directly targeted by *miR-195*, which cause to cell cycle's arrestment at the G1 phase. *miR-195* also targets *Survivin*, which is also called *BIRC5* (Figures 5 and 6).[79] One of the direct and functional targets of *miR-195* is *IGF1R*, which is crucial for tumor transformation and survival of LC cells and plays a critical role in regulating different cellular processes, such as differentiation, survival, motility, and growth. In LC cells, *IGF1R* is generally overexpressed and plays a significant role in tumorigenesis.[82]

## 2.9 | MicroRNA-203

*miR-203* is located on 14q32.33 and is involved in skin diseases. *miR-203* is also served as a TS microRNA by regulating different biological processes including differentiation, metastasis, invasion, cell mobility, and apoptosis in various cancers, such as LC.[53,83,84]

*miR-203* functions as TS microRNA by directly targeting *Bmi1* in NSCLC cells. *Bmi1* is a member of a Polycomb group (PcG) multiprotein PRC1-like complex. *miR-203* is downregulated but *Bmi1* is upregulated in NSCLC cells. Overexpression of *miR-203* suppresses *Bmi1* expression, which causes inhibition of proliferation and growth in NSCLC cells.[85]

Cluster of Differentiation 82 (*CD82*) is a metastasis suppressor. *CD82* prevents the Wnt signaling pathway through downregulation of Frizzled (FZD) isoforms, which is a family of GPCR proteins that act as receptors in the Wnt signaling pathway. *CD82* causes the upregulation of *miR-203* and directly downregulates Frizzled2 (*FZD2*) expression.[86] *miR-203* directly identifies and binds to 3′-UTR of *SRC* mRNA and inhibits *SRC* translation. SRC protein acts as an oncogene and is involved in tumor progression through promoting the proliferation, survival, and invasion of LC cells. SRC protein also regulates several signaling pathways related to tumor progression and development, such as the FAK signaling pathway that is also known as PTK2, which is involved in cellular spreading and adhesion processes. *SRC* expression is inhibited by *miR-203*, which activates the suppression of the SRC/Ras/ERK signaling pathway, which finally suppressed the migration, invasion, and induced the apoptosis of LC cells (Figure 4).[87]

*PKCα* is a direct target of *miR-203*. PKC involved in different signal transduction pathways. The PKC family encloses ten associated isoforms with different cofactor requirements. The level of PKCα protein is higher in NSCLC cells compared with normal cells; thus, one of the general features of NSCLC cells increased the expression of *PKCα*. *miR-203* identifies the 3′-UTR of the *PKCα* mRNA and downregulates its expression in LC cells (Figure 6).[88]

*RGS17* is a direct and functional target of *miR-203*. Interestingly, upregulation of *miR-203* suppresses the growth of LC cells through inhibiting *RGS-17* in transcription level. *RGS-17* is located on 6q25.3 and encodes a member of the RZ family of RGS proteins, which is reported to be overexpressed in different cancers, such as hepatocellular carcinoma and human LUAD. RGS protein increases the rate of GTP hydrolysis. Moreover, the increased expression level of RGS17 protein has been positively associated with tumor cell proliferation through the CAMP-PKACREB pathway in human LC.[89]

## 2.10 | MicroRNA-218

*miR-218* is located on 4p15.31 and 5q35.1 and is recognized as TS microRNA in NSCLC. *miR-218* is co-expressed simultaneously with its host genes. Slit Homolog 2 Protein and Slit Homolog 3 Protein are two members of the *SLIT* family and are the host genes of *miR-218*. Aberrant expression of *miR-218* is reported in various cancers, such as bladder and NSCLC.[90,91]

Tumor protein D52 (*TPD52*) is directly regulated via *miR-218*. TPD52 protein is involved in plasma membrane-based exocytic and endocytic function in LUAD. One of the most important amplified genomic regions is 8q21.13, which includes *TPD52* gene. Overexpression of *TPD52* is reported in SCLC, LUAD, and LUSC. Overexpression of *TPD52* is detected in LUSC clinical specimens. Furthermore, downregulation of the *TPD52* gene inhibited cancer cell invasion and metastasis. *miR-218* can inhibit invasion and migration of LC by directly targeting 3′-UTR of the *TPD52* gene.[92]

*miR-218* plays an antimetastatic role, which is on the basis of inhibiting cell invasion and migration in NSCLC cells through directly targeting *HMGB1*. Overexpression of *HMGB1* is related to cancer cells migration and is involved in the development of different cancers including melanoma, colon, and LC. *HMGB1* promotes the cell invasion through regulation of *MMP-9* in LC. Moreover, *miR-218* suppresses *HMGB1* expression

and reduces invasion and migration of LC cells through regulation of *MMP-9*.[93]

EMT and EMT-related traits are inhibited by overexpression of *miR-218* through targeting the *ZEB2* and *Slug* (*Snail 2*), which is an EMT regulator, in vivo and in vitro. *Slug* and *ZEB2* are known to be related to EMT and tumor metastasis. *miR-218* downregulates *Slug* and *ZEB2* expression level by directly targeting their 3′-UTR regions (Figures 4 and 6). Furthermore, the high expression level of *miR-218* increases the chemo-sensitivity of H1299 cells to cisplatin by suppression of *ZEB2* and *Slug*.[94]

*EGFR* is a direct target of *miR-218*. The correlation between EGFR protein levels and *miR-218-5p* is an inverse correlation in NSCLC. The expression of *EGFR* is negatively regulated by *mir-218*, which leads to inhibiting EGFR translation in NSCLC (Figure 3).[95]

*MEF2D* is a direct target of TS *miR-218*. MEF2 proteins involved in gene expression, stress response, cellular differentiation, and embryonic development. *MEF2D* is overexpressed in LC tissues and cell lines. Furthermore, transcription of *MEF2D* is negatively regulated by *miR-218* in LC cells. The high expression level of *miR-218* suppresses the expression of *MEF2D* in LC cells, which cause to inhibition of cancer cells development.[96]

## 2.11 | MicroRNA-320

The *miR-320* family is a highly conserved microRNA but only found in vertebrates. This family contains five members: *miR-320-a, miR-320-b, miR-320-c, miR-320-d*, and *miR-320-e*. *miR-320-d* and *miR-320-e* exist only in humans and primates. The *miR-320a* is located on 8p21.3, whereas the *miR-320b-1* and *miR-320b-2* are located on 1p13.1 and the *miR-320c-1* and *miR-320c-2* are located on 18q11.2. *miR-320* is downregulated in different tumors compared with normal tissue, for instance, in prostate cancer and NSCLC.[97-100]

*miR-320a* is an important TS microRNA that increases the sensitivity of cancer cells to chemotherapy. *miR-320a* directly regulated *STAT3* expression in LUAD cells (Figure 3). *STAT3*, a member of the JAK/STAT3 signaling pathway, is the most important player in several pathological and physiologic processes, such as cell survival, growth, and proliferation in different cancers as well as in immune diseases. *miR-320a* suppresses *STAT3* signals and suppression of *STAT3* signals induce apoptosis and reduce cell proliferation.[101]

*miR-320* inhibits NSCLC cells invasion and migration through directly targeting Fas cell surface death receptor (*FAS*), which is an essential protein for cancer metastasis, invasion, and proliferation. The *FAS* gene encodes a protein named TNFSF6, a multifunctional enzymatic complex. In normal human tissue, the endogenous *FAS* is expressed at low levels. Nevertheless, the expression level of *FAS* is extremely upregulated in cancer cells, which leads to metastasis and proliferation of different types of cancer, such as colorectal, bladder, and LC. In addition, the expression of *FAS* at the translational level reduced through *miR-320* expression in NSCLC cells. In conclusion, *miR-320* acts as TS in NSCLC cells via directly targeting *FAS*.[98]

*SND1* acts as a metastasis activator and directly targeted by *miR-320a* in LC cells (Figure 5). *SND1* also known as *p100* is an endonuclease that mediates microRNA decay of both protein-free and AGO2-loaded microRNAs and acts as a transcriptional coactivator for STAT5. *P100* is upregulated in human LC cells and is involved in cancer cell metastasis and invasion. *P100* is directly targeted by *miR-320a* through its 3′-UTR binding site, which leads to inhibition of *P100* and reduces metastasis and invasion of LC cells.[102]

## 2.12 | MicroRNA-449a

*miR-449a* is located on 5q11.2, which is an important recognized region in different cancers, such as LC. *miR-449a* is recognized as TS microRNA. *miR-449a* is downregulated in different types of cancers including bladder cancer and endometrial cancer.[103]

*miR-449a* acts as an important metastasis suppressor in various cancers. Overexpression of *miR-449a* suppresses migration and invasion of NSCLC cells. Furthermore, *miR-449a* mediates the metastasis-suppressing activity of NSCLC cells via modulating Polycomb Repressive Complex 2 Subunit (*SUZ12*) expression. You et al[104] indicated that Mitogen-activated protein kinase 1 (*MAP2K1* or *MEK1*) is a direct and functional target of *miR-449a*. Moreover, the MAPK signaling pathway is involved in NSCLC metastasis that regulated by *miR-449a*. Interestingly, *miR-449a* expression is directly regulated by Activator protein 1 (AP-1) through a negative feedback loop (Figure 4). AP-1 is an important TF which regulates gene expression level in response to different stimuli including stress, and cytokines. *miR-449a* plays a TS function through targets the *E2F3* gene, which results in inhibition of cell proliferation and induction of cell senescence-like phenotype in LC cells. *E2F3* is a member of the E2F family that is frequently dysregulated during tumorigenesis and overexpressed in different cancers, such as LC. E2F3 is an important regulator of G1 to S transition and has a major role in regulating both cell proliferation and apoptosis. *E2F3* is overexpressed in almost all LC tumors and cell lines. The *E2F3* gene is downregulated by overexpression of *miR-449a* in LC cells, which leads to suppression of G1/S transition of cancer cells.[105]

## 2.13 | Drug-resistance in lung cancer

The main cause for chemotherapeutic failure is drug-resistance (DR). Chemotherapy is the principal treatment for patients with LC. Multidrug resistance (MDR) is one of the main factors that makes the outcome undesirable. Chemotherapy is considered as the first strategy for the treatment of LC. Wide molecular profiling studies identify the different drug-gable target for LC therapy. A variety of effective therapeutic molecules is specifically targeting signaling pathways and oncogenic mutations driving lung carcinogenesis have been successfully tested and developed in the clinical filed. Nevertheless, because of the detected DR, the effectiveness of chemotherapy is extremely limited, which results in poor survival rate. Several molecular mechanisms, such as changes in drug targets, mutations restoring DNA repair function, high drug efflux, deregulated apoptosis, and activation of survival signaling pathways contribute to DR. Aberrant regulation of microRNA affects the expression of genes involved in DR mechanisms including DNA damage repair, cell cycle control, and apoptosis.[106]

## 2.14 | MicroRNA-7

According to Liu et al[111] reports, in patients with SCLC, the downregulation of miR-7 is not related to sex, age, and stage of SCLC. It correlates with the survival rate and the reaction of patients to drugs. Multidrug resistance-associated protein 1 (MRP1) is an important protein in DR of different cancers and is encoded by the *ABCC1* gene (Table 1). There is a reverse correlation between the expression of MRP1 and *miR-7*. Interestingly, in SCLC cells expression level of MRP1 is downregulated by overexpression of *miR-7*. Provide evidence endorse that *miR-7* suppresses MRP1 with binding to 3′-UTR of its gene. Therefore, it mediates SCLC chemoresistance, which is a significant procedure of chemoresistance, potential therapeutic target, and prognostic predictor SCLC.

## 2.15 | MicroRNA-16

Paclitaxel-based on combination chemotherapy is used widely, which may prolong survival in patients with LC. Chatterjee et al[112-114] reported that in paclitaxel-resistant LC cells, *miR-16* is significantly downregulated. Paclitaxel stabilizes microtubule and arrests mitosis. Furthermore, paclitaxel is the cause of apoptosis in LC cells by regulation of expression of the cytokine gene and interacting with the membrane proteins of Mitochondria. Chatterjee et al show that one of the targets of *miR-16* in paclitaxel-resistant LC cells is *Bcl-2*. Therefore, Over-expression of *miR-16* remarkably decreases the expression of Bcl-2. Overexpression of *Bcl-2* is found in various cancers and is connected with the expansion of chemoresistance in LC. In addition, it is discovered that if *miR-16* overexpresses and paclitaxel is used for treatment enormously, the paclitaxel-resistant LC cells sensitize to paclitaxel. Therefore, they are led to apoptosis through the caspase-3 pathway. *Bcl-2* overexpressed is related to the development of chemoresistance in LC cells (Table 1). *Bcl-2* expression is significantly reduced by Overexpression of *miR-16*.

## 2.16 | MicroRNA-26a/b

Chen et al[109] show that *EZH2* is a direct and functional target of *miR-26a* (Figure 4). In docetaxel-resistant LUAD cells overexpression of *miR-26a* downregulates *EZH2*, which reduces cell growth and proliferation and increases apoptosis. Furthermore, downregulation in *EZH2* expression reverses EMT (Table 1). The *miR-26a/EZH2* signaling pathway involved in the malignancy of docetaxel-resistant LUAD cells showed that *miR-26a* involve in the molecular etiology of chemoresistant LUAD cells.

## 2.17 | MicroRNA-29c

Sun et al[59] show that oncogene *AKT2* is a functional and direct target of *miR-29c* and is negatively regulated by this microRNA (Figures 4 and 6). *AKT2* encodes

**TABLE 1** Drug resistance microRNAs in LC

| MicroRNA | Target | Protein name | Cancer | Signaling pathway | Ref |
|---|---|---|---|---|---|
| **MicroRNA-7** | ABCC1 | Multidrug resistance-associated protein 1 (MRP1) | SCLC | --------- | 107 |
| **MicroRNA-16** | Bcl-2 | Bcl-2-like protein 2 | NSCLC | PI3k/AKT, IL-6/JAK/STAT3 | 108 |
| **MicroRNA-26a/b** | EZH2 | Histone-lysine N-methyl transferase EZH2 | LUAD | ERK and FAK | 109 |
| **MicroRNA-29c** | AKT2 | RAC-beta serine/threonine-protein kinase | NSCLC | AKT and mTOR | 59 |
| **MicroRNA-148** | DNMT1 | DNA (cytosine-5)-methyl transferase 1 | NSCLC | --------- | 110 |

Abbreviation: LC, lung cancer.

RAC-beta serine/threonine-protein kinase in humans, which regulate several processes, such as angiogenesis, proliferation, and cell growth (Table 1). Furthermore, the PI3K/Akt signaling pathway is negatively regulated by *miR-29c*, which leads to cisplatin sensitivity of NSCLC cells. *miR-29c* overexpression significantly raises the cisplatin sensitivity of NSCLC cells. Nevertheless, cisplatin resistance of NSCLC cells is increased by knocking down of *miR-29*. *AKT2* and *Antigen ki-67* index expression is decreased by both *miR-29c* overexpression and cisplatin treatment in NSCLC cells. Ki-67 is an important protein encoded by the Marker of Proliferation Ki-67 (*MKI67*) gene in humans. In conclusion, co-treatment of NSCLC cell with cisplatin and *miR-29c* inhibit migration and invasion.

### 2.18 | MicroRNA-148

Su et al[110] compared cisplatin resistant NSCLC cell line (A549/DDP) and parental A549 cell line. The findings showed the downregulation of *miR-148b* and contrary to its upregulation of *DNMTs*. Interestingly, overexpression of *miR-148b* is the cause of the decline in the expression of *DNMT1* in A549 and A549/DDP cells. Besides, they increase cisplatin sensitivity of A549/DDP cells and lead them to apoptosis. Nevertheless, an inhibitor of *miR-148b* enhances *DNMT1* expression (Table 1). In sum, over-expressed *DNMT1* inverts pro-apoptosis impact of *miR-148b* and silenced *DNMT1* increases the sensitivity of A549/DDP cells to cisplatin.

## 3 | CONCLUSION

Different expressions for several microRNAs have been discovered in LC. These different expressions are tumor- and tissue-specific. This review can shed light on accomplishing diagnosis and treatment of LC. Therefore, establishing a signature microRNA expression profile on the basis of detailed studies of different microRNAs and their targets can help its prognosis, early diagnosis, and classification. In addition, probably the novel strategies for the treatment of LC may be offered by focusing on aberrations in the expression of microRNAs and how they may be regulated. According to above-mentioned research, distinct microRNA expression profiles in the body fluids and exhaled breath of patients with LC have been identified which can act as potential exhaled breath and blood-based biomarkers for LC diagnosis.

Furthermore, the expression level of distinct microRNAs increases in body fluids and exhaled breath of patients with metastatic LC compared with patients with non-metastatic LC. As a result, they are suggested as new prognostic markers. Therefore, to diagnose LC precisely, it is possible that microRNAs combined with other diagnostic tests can be used jointly as potential biomarkers. Despite being in the early developmental stages towards these novel therapeutic strategies, on the basis of the most recent research, we believe that some microRNAs should be served as potential therapeutic tools for monotherapy or combination therapy of LC with available medical treatments and could be promising in terms of therapeutics in near future. Because of the tumor suppressive properties of microRNAs, they are likely to be used as therapeutic targets and biomarkers for LC treatment because cancer is not defeated without a fight.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS

VAA did initial design and design, wrote the manuscript, and is the first author. ES reviewed and presened criticism. BM designed and initiated ideas, collaborated in drafting, editing, and review. AM did image design. BB did initial design and design, review and critique, and gave the final approval of the paper for publication.

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